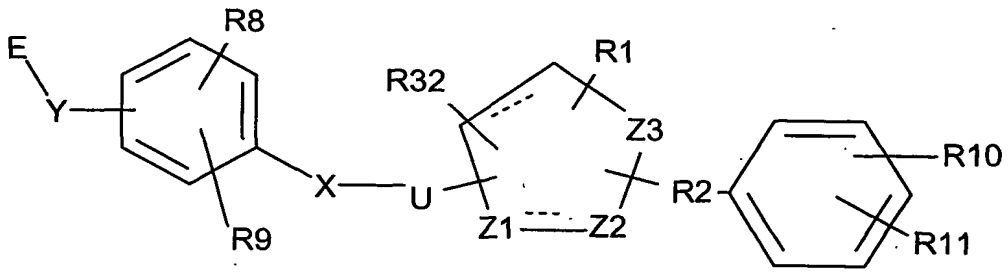
CLAIMS

What is claimed is:

1. A compound of the Formula I':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18,

R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;

(f) Y is selected from the group consisting of C, NH, and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4

cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;

(h) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(i) Z3 is selected from the group consisting of N, O, and C;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are

each optionally substituted with from one to three independently selected from R28;

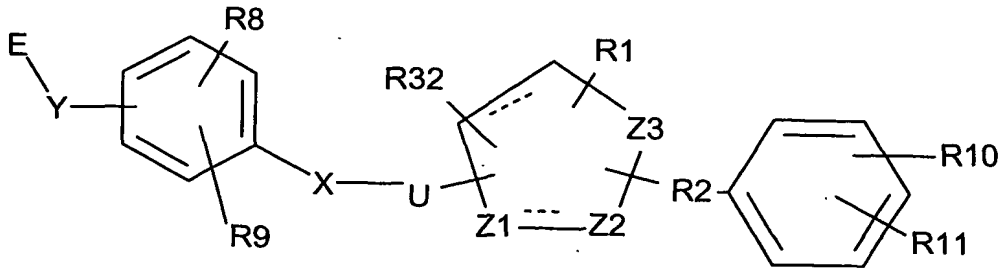
(m) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo; and

(p) ---- is optionally a bond to form a double bond at the indicated position.

2. A compound of the Formula I'':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-

alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R30;

(f) Y is selected from the group consisting of C, O, S, NH and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;

(h) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(i) Z3 is selected from the group consisting of N, O, and C;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three

independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

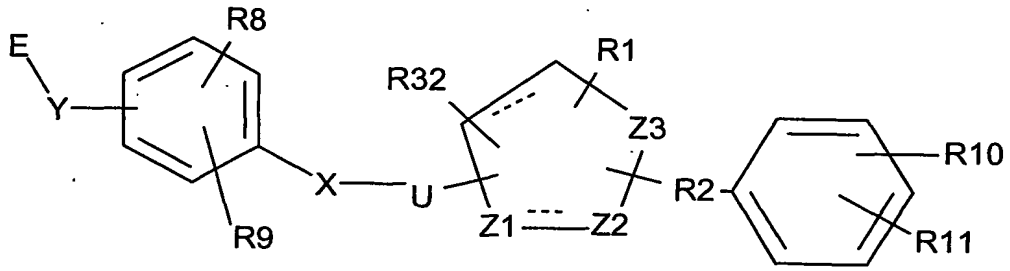
(m) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo; and

(p) ---- is optionally a bond to form a double bond at the indicated position.

3. A compound of the Formula I''':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19,

$NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;

(f) Y is selected from the group consisting of O, S, C, NH and a single bond;

(g) E is C(R3)(R4)A; wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6

cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;

with the proviso that when Y is O then R4 is selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26;

(h) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(i) Z3 is selected from the group consisting of N, O, and C;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano,

nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

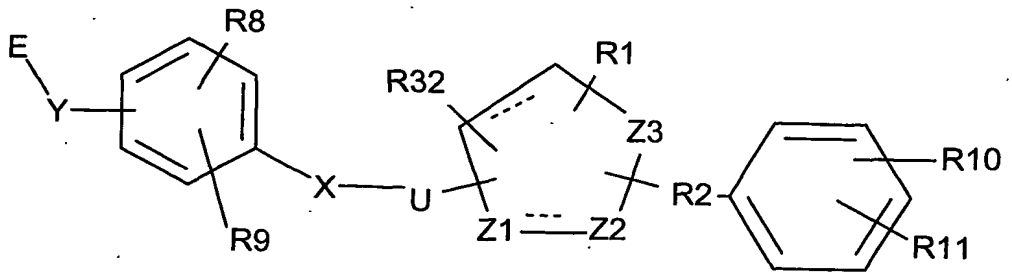
(m) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo; and

(p) ---- is optionally a bond to form a double bond at the indicated position.

4. A compound of the Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each

independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker may be replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with R30;

(f) Y is selected from the group consisting of C, O, S, NH and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally

substituted with from one to three substituents each independently selected from R26;

(h) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(i) Z3 is selected from the group consisting of N, O, and C;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-

alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

(m) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo; and

(p) ---- is optionally a bond to form a double bond at the indicated position.

5. A compound as claimed by any one of Claims 1 through 4 wherein X is -O-.

6. A compound as claimed by any one of Claims 1 through 4 wherein X is -S-.

7. A compound as claimed by any one of Claims 2 through 6 wherein Y is O.

8. A compound as claimed by any one of Claims 2 through 6 wherein Y is C.

9. A compound as claimed by any one of Claims 1 through 6 wherein Y is S.

10. A compound as claimed by any one of Claims 1 through 9 wherein Z3 is N.

11. A compound as claimed by any one of Claims 1 through 9 wherein Z3 is O.

12. A compound as claimed by any one of Claims 1 through 11 wherein Z2 is N.

13. A compound as claimed by any one of Claims 1, through 12 wherein Z1 is C.

14. A compound as claimed by any one of Claims 1 through 12 wherein Z1 is N.

15. A compound as claimed by any one of Claims 1 through 12 wherein Z1 is O.

16. A compound as claimed by any one of Claims 1 through 15 wherein ---- is a bond to form a double bond at the designated location on Formula I.

17. A compound as claimed by any one of Claims 1 through 16 wherein E is C(R3)(R4)A.

18. A compound as claimed by any one of Claims 1 through 17 wherein A is COOH.

19. A compound as claimed by any one of Claims 1 through 18 wherein R10 is haloalkyl.

20. A compound as claimed by any one of Claims 1 through 18 wherein R10 is CF_3.

21. A compound as claimed by any one of Claims 1 through 18 wherein R10 is haloalkyloxy.

22. A compound as claimed by any one of Claims 1 through 18 wherein R10 and R11 are each independently selected from the group consisting of hydrogen, halo, oxo, C_1-C_6

alkyl, C_1-C_6 alkyl-COOR12'', C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkyloxy.

23. A compound as claimed by any one of Claims 1 through 18 wherein R10 is selected from the group consisting of C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and aryloxy.

24. A compound as claimed by any one of Claims 1 through 23 wherein R1 is optionally substituted C2-C3 arylalkyl.

25. A compound as claimed by any one of Claims 1 through 23, wherein R8 and R9 are each independently selected from the group consisting of hydrogen and C_1-C_3 alkyl.

26. A compound as claimed by any one of Claims 1 through 23 and 25 wherein R1, R2, R3, and R4 are each independently selected from the group consisting of C_1-C_2 alkyl.

27. A compound as claimed by any one of Claims 1 through Claim 23 and 25 wherein R1, R3, and R4 are each independently selected from the group consisting of hydrogen and C_1-C_2 alkyl.

28. A compound as claimed by any one of Claims 1 through 25 or Claim 27 wherein R2 is a bond.

29. A compound as claimed by any one of Claims 1 through 28 wherein U is C_1-C_3 alkyl.

30. A compound as claimed by any one of Claims 1 through 29 wherein U is saturated.

31. A compound as claimed by any one of Claims 1 through 30 wherein U is substituted with C_1-C_3 alkyl.

32. A compound as claimed by any one of Claims 29, 30 and 31 wherein one carbon of the aliphatic linker is replaced with an O.

33. A compound as claimed by any one of Claims 1 through 31 wherein U is an aliphatic linker having one carbon replaced by S.

34. A compound as claimed by any one of Claims 1 through 33 wherein the aliphatic linker is substituted with from one to three substituents each independently selected from R30.

35. A compound as claimed by Claim 34 wherein the aliphatic linker is substituted with from one to two substituents each independently selected from R30.

36. A compound as claimed by any one of Claims 1 through 35 wherein each R30 is independently selected from the group consisting of C1-C6 alkyl.

37. A compound as claimed by any one of Claims 1 through 36 wherein each R30 is independently selected from the group consisting of C2-C3 alklyl.

38. A compound as claimed by any one of Claims 1 through 37 wherein R30 is selected from the group consisting of aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl.

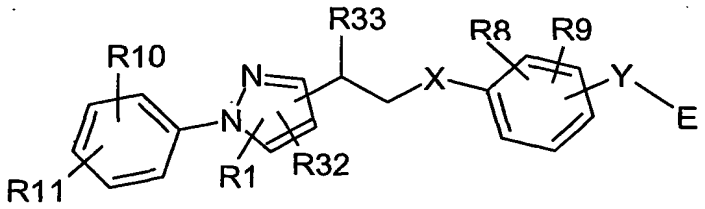
39. A compound as claimed by any one of Claims 1 through 38 wherein "---" each form a double bond in the five membered ring, Z2 and Z3 are each N and Z3 is bonded to R2.

40. A compound as claimed by Claim 39 wherein Y is O and E is $-CH_2COOH$.

41. A compound as claimed by any one of Claims 1 through 40 wherein U is substituted with methyl.

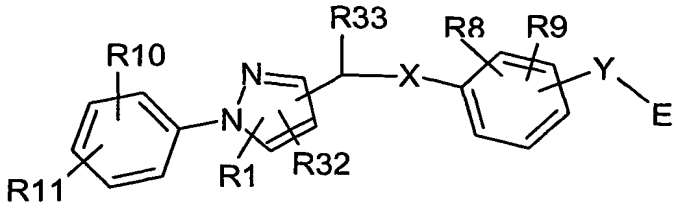
42. A compound as claimed by any one of Claims 1 through 41 wherein U is methylene.

43. A compound as claimed by any one of Claims 1 through 10, one of Claims 17 through 25, or one of Claims 27 through 35 represented by the following Structural Formula II:



wherein R33 is selected from the group consisting of hydrogen and C_1-C_3 alkyl.

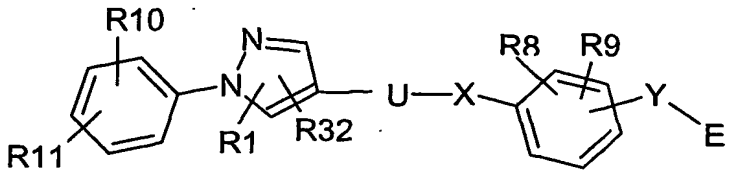
44. A compound as claimed by any one of Claims 1 through 10, or one of Claims 17 through 36 represented by the following Structural Formula III:



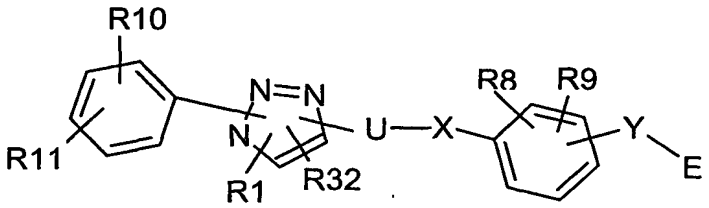
wherein R33 is selected from the group consisting of hydrogen and C_1-C_3 alkyl.

45. A compound as claimed by any one of Claims Claims 1 through 10, or one of Claims 17 through 42 represented by the following

Structural Formula IV:



46. A compound as claimed by any one of Claims 1 through 10 or one of Claims 17 through 42 represented by the following Structural Formula V:



47. A compound as claimed by any one of Claims 1 through 46 wherein X and Y are substituted at a 1,4-position, such that X and Y are para substituted to one another.

48. A compound as claimed by any of of Claims 1 through 46 wherein X and Y are substituted at a 1,3-position, such that X and Y are meta substituted to one another.

49. A compound as claimed by any one of Claims 1 through 4 wherein the compound is selected from the group consisting of

{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid;

3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid;

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenoxy)-acetic acid;

(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-propionic acid;
(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;
(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;
(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;
(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;
(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;
(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;
(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-acetic acid;
{3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenyl}-acetic acid;
(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-acetic acid;
2-(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;
(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-acetic acid;
(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;

(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;

(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;

(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;

(S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;

(R)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;

(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;

(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;
(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;
(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;
{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;
{4-[1-(3,5-Bis-trifluoromethyl-phenyl)-5-methyl-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;
(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid;
3-(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid;
3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid;
{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;
{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;
3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid;
{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid;

3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid;

(S)-3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid;

{3-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid;

3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid;

3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid;

{2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid;

[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid;

[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid;

3-[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethoxy)-phenyl]-propionic acid;

{2-Methyl-4-[1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

{2-Methyl-4-[5-methyl-1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

{4-[1-(3,5-Bis-trifluoromethyl-benzyl)-5-phenyl-1H-[1,2,3]triazol-4-ylmethanesulfonyl]-2-methyl-phenoxy}-acetic acid;

3-(2-Methyl-4-{1-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethoxy}-phenyl)-propionic acid;

3-{2-Methyl-4-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-ylmethoxy]-phenyl}-propionic acid;
{4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid; {4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;
{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenoxy}-acetic acid; and
3-{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid.

50. A compound as claimed by any one of Claims 1 through 4 which is a compound of Formula I selected from the group consisting of(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid,(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid, (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid, and (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid.

51. A compound as claimed by any one of Claims 1 through 4 which is(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid.

52. A compound as claimed by any one of Claims 1 through 50 that is the S conformation.

53. A compound as claimed by any one of Claims 1 through 50 that is the R conformation.

54. A pharmaceutical composition, comprising as an active ingredient, at least one compound as claimed by any one of Claims 1 through 53 together with a pharmaceutically acceptable carrier or diluent.

55. A method of modulating a peroxisome proliferator activated receptor, comprising the step of contacting the receptor with at least one compound as claimed by any one of Claims 1 through 53.

56. A method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 53.

57. A method of treating metabolic disorder in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 53.

58. A method of Claim 57 wherein the mammal in need thereof is diagnosed as suffering from metabolic disorder.

59. A method of selectively modulating a PPAR delta receptor comprising administering a compound as claimed by any one of Claims 1 through 53 to a mammal in need thereof.

60. The manufacture of a medicament for use in the treatment and/or prevention of a condition mediated by nuclear receptors, in particular by a peroxisome proliferator activated receptor, wherein the compound is a compound as claimed by any one of Claims 1 through 53.

61. A method of treating atherosclerosis in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least one compound of Claims 1 through 53.

62. A compound as Claimed by any one of Claims 1 through 53 for use as a pharmaceutical.

63. A method for treating or preventing the progression of cardiovascular disease in a mammal in need thereof comprising administering a therapeutically effective amount of a compound as Claimed by any one of Claims 1 through 53.

64. A method as claimed by Claim 63 wherein the mammal is diagnosed as being in need of such treatment.

65. A compound as claimed by any one of Claims 1 through 53 wherein the compound is radiolabeled.

66. A compound as disclosed by any one of the Examples herein.

67. All methods disclosed herein of preparing the compounds represented by Structural Formula I.